Noncoding RNAs in Cell Fate Determination

Grant Award Details

Noncoding RNAs in Cell Fate Determination

Grant Type: New Faculty I

Grant Number: RN1-00529

Project Objective: The overall goal of this research is to understand the epigenetic control of cell fates, centered on the interplay of chromatin states and long intergenic non-coding RNAs (lincRNAs). The central hypothesis of this research program is that lincRNAs are
key guides for specific changes to chromatin states that accompany different cell fates. The major areas of progress have been (i) discovery of a new function of lincRNAs in controlling the longevity of chromatin state and thus stability of cell fates; (ii) a new technology for genome-wide mapping of lincRNA-chromatin interactions (invention disclosure will be submitted in October 2012).

Investigator:

Name:	Howard Chang
Institution:	Stanford University
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,985,894

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: Noncoding RNAs in Cell Fate Determination

Public Abstract:

The human body is composed of thousands of cell types, which all came originally from embryonic stem cells. Although all these cell types have the same genetic blueprint, different genes are active in different cells in order to give each its distinctiveness. The process by which the genes remember whether they are in liver, brain, or skin cells is called “epigenetics.” A central problem in regenerative medicine is to understand the epigenetic program so that human embryonic stem cells can be efficiently turned into the cell types required for each specific patient. Conversely, by manipulating the epigenetic program, adult cells may be reprogrammed into primitive cells that can turn into other cell types to repair diseased or damaged tissues.

The goal of the proposed research is to better understand the epigenetic program in human embryonic stem cells and adult cells. We want to tap into the natural mechanisms by which the body normally “remembers” what kinds of cells reside in each tissue and apply them to regenerative therapies. Specifically, the research will study the roles of a newly discovered type of genes, termed “noncoding RNAs”, in stem cell epigenetics.

A better understanding of how cells remember their own fates can improve regenerative medicine in several ways. First, by appreciating the roles of noncoding RNAs in this process, specific noncoding RNAs can be used as markers to track and predict when cells are acquiring or forgetting specific cell fates. For instance, it may be possible to learn from the pattern of noncoding RNAs that an embryonic stem cell is ready to become brain cells, which can be used to treat a patient with stroke. Second, beyond tracking cell fate, noncoding RNAs may be used to directly manipulate stem or adult cell fates. By introducing noncoding RNAs from different cell types, embryonic stem cells or adult cells may be directly reprogrammed into the desired cell type. While these potential application are far in the future, we believe that better knowledge of this new level of gene regulation will one day lead to more facile and efficient manipulation of cell fates for regenerative medicine.

Statement of Benefit to California:	The proposed research can benefit the state of the California in three ways. First, the research will generate important knowledge on new ways to manipulate cell fate potentials of stem cells and mature adult cells. The focus of this research is to explore the genetic circuitry that locks cells into particular fates, whether it is to become skin, muscle, or brain. Better understanding of these circuitries could allow human embryonic stem cells to be directed to become particular tissues—and remember such instructions permanently. Alternatively, interference with these circuitries could allow adult cells to be reprogrammed into stem cells, where they can be used to generate damaged tissues. This information could speed the development of regenerative medicine in California, benefiting patients with currently untreatable diseases. Second, the proposed research will generate new tools for stem cell research and regenerative medicine. As a direct result of this work, we will provide a complete genetic and epigenetic characterization of some of the first human embryonic stem cells created in California. This information will allow future investigators, physicians, and potential patients to better utilize them in research and therapy, or conversely appreciate potential limitations or risks associated with these embryonic stem cell lines. Moreover, we are likely to generate derivatives of these embryonic stem cell lines that have altered potential to become specific cell types. Such cell lines with properties of “directed differentiation” may be particularly useful for treatment of diseases where deficits of specific cell types are known. Finally, the proposed research will train young scientists to become skilled in human stem cell research. Graduate Ph.D. students and postdoctoral fellows in this California-based institution will gain the hands-on experience and expertise of manipulating human stem cells and of reprogramming adult cells. The training and experience of these young scientists will prepare them to develop new regenerative therapies, launch new companies based on stem cells, or teach future students about regenerative medicine. Creating a cadre of well-trained individuals would be a vital step toward making California a central hub for regenerative medicine.